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The Influence of Vitamin E on Vascular Disease: In 1942 Mason reported that the classical fetal resorption in vitamin E-deficient pregnant rats was due to such vascular abnormalities in the uterine wall as stasis, distention, and thrombosis (notably venous). Occasionally these conditions terminated in ruptures into the decidua with frank hemorrhage. In E-deficient chicks analogous phenomena are also seen, and there is some evidence in them, too, of functional alteration of the capillary walls.

At about the same time, E. V. Shute, one of the authors of this article, stated that senile vulvovaginitis treated with high doses of the tocopherols often was improved clinically. Biopsy of vulvar tissue after such treatment revealed an appearance suggesting either the proliferation of new capillaries or the reopening of old collapsed capillaries. But the definite lag of from 2 to 4 weeks before improvement showed itself suggested the former as being the more likely. On a priori physiological grounds it was the more tenable explanation, too.

Mason has also pointed out that in both the monkey and hamster vascular degeneration is a prominent feature in the picture of prolonged vitamin-E deficiency. Shute has recently reported the rapid response to intensive tocopherol therapy of 3 patients with acute hemorrhagic nephritis, indicating an effect on the glomerular capillaries. Other observations made on the purpuras by the authors indicate that the tocopherols decrease capillary permeability and increase low platelet counts. However, it was the influence of the tocopherols on coronary thrombosis and other cardiac processes that recently turned the attention of the authors directly to the effect of tocopherols upon pathological conditions of the vascular system. It was noted that many arteriosclerotic cardiacs given tocopherols reported that feet and hands that had been cold and numb for years had suddenly become warm again. Many had had small indolent ulcers which now healed rapidly. In following up such clues the authors investigated certain types of peripheral vascular disease in a series of patients in whom tocopherol therapy was used.

Thrombophlebitis and phlebothrombosis. Twenty-two cases of this condition were studied. All patients were treated successfully with tocopherols. The authors ascribe the results achieved in thrombosis of the veins, with or without attendant inflammation, to a direct effect of the tocopherols on thrombi. There seems to be little doubt that in a fresh thrombosis the clot itself is directly attacked; it can literally melt away. But in thrombophlebitis a thick thrombus can be felt long after all evidences of inflammation other than an elevation of the sedimentation rate have disappeared. Resolution always seems to begin and to progress uniformly over thrombotic areas of any length. Any associated fever usually falls promptly. The possibility of embolism following unduly rapid resolution of a fresh phlebothrombosis must be borne in mind, of course. Perhaps in such cases a small dose of tocopherols and a more gradual response would be desirable.

Fresh thrombi are often associated with a low platelet count, as if the fresh fibrin plug had formed a screen to take a large share of the platelets

out of circulation. Clinical improvement in these patients is coincident with a rise in platelet count and an apparent resorption of the fibrin mesh. On the other hand, older and organized thrombi are usually associated with higher platelet counts, do not seem to screen out platelets, and do not respond to the same dosage of tocopherols. Perhaps double the usual dose is required - often as high as 600 milligrams of the alpha form. Can it be that tocopherols attack fibrin directly by a proteolytic process? A decrease of platelets and a persisting high sedimentation rate on tocopherol therapy is an indication either of recurrence or extension, and demands an increased dose.

Should all puerperal women be given tocopherols in an effort to avoid thrombosis? Similarly, many patients, after herniotomies and pelvic operations might benefit from prophylactic dosage.

Indolent ulcers of the leg and ankle. In the thirteen patients whose cases were studied the response achieved was both prompt and lasting. It was ascribed to an improvement in local arteriolar circulation and to better oxygen utilization by the local tissues. During treatment the affected extremity sometimes became warmer than its mate. These studies may bear on the problems of plastic surgery.

Early gangrene of the extremities. Three such cases were studied. The first patient with early gangrene of an extremity treated with tocopherols was a woman of 76 years of age, who was admitted to the hospital 8 December 1946 for an acute diverticulitis which was promptly operated upon. Her left leg at that time showed early but discrete and superficial gangrenous areas extending as high as the knee. She was a mild diabetic under good dietary control, but with arteriosclerosis. After 11 December she was given 100 milligrams of alpha tocopherol per day by mouth, and soon showed great improvement in the affected leg. She was discharged from hospital on 22 December 1946 and has led an active life ever since, doing her own housework. She still takes 25 milligrams of alpha tocopherol per day as a prophylactic measure. There has been no recurrence of her lesions.

What would tocopherol therapy do for frostbite, "immersion foot," and similar conditions?

Thromboangiitis obliterans and related vascular conditions. One verified and one dubious case of thromboangiitis obliterans were thoroughly studied. The dubious case might, more accurately, have been called Raynaud's disease. However, in it vascular relief was achieved. In the other typical case there was a fine result. It should be mentioned that patients with such conditions often suffer as their circulation improves. During that time they may be difficult to maintain on treatment.

A former colleague of the authors, Dr. C. K. Stuart, has treated with tocopherols 4 patients displaying intermittent claudication, the results being excellent in 3 of them. Also, Dr. George Dowd, has treated 4 such patients

between the ages of 48 and 63 years. Three of the patients became asymptomatic and one was markedly improved on doses of from 400 to 1100 milligrams of mixed tocopherols daily. The authors have had a good result in the only case they have treated.

Cerebral thrombosis. One of the more puzzling phases of these studies has been the trivial influence the tocopherols usually exert on hypertension per se, but in hypertensive heart disease there may be a small initial rise of both systolic and diastolic blood pressures coincident with increased cardiac tone and relief of decompensation, which is often followed by a drop as compensation occurs. The symptoms ascribable to hypertension are often relieved out of all proportion to the improvement thus achieved. This parallels the experience of Smithwick with his surgically treated hypertensives.

The authors have studied a score of cases of cerebral thrombosis, most of them of months', or as long as 2 and 1/2 years' standing. Even in the old cases some improvement was often achieved. As would be anticipated, the patients treated most promptly did best. Generally speaking, from 10 to 75 per cent of the disability has disappeared in the group as a whole. This gain was made principally within the first 3 weeks, after which improvement went on much more slowly. It is very difficult, of course, to prove how much of the gain was attributable to tocopherol therapy and how much was spontaneous. Dowd has said that he has seen definite improvement in a woman whose stroke occurred 6 years previously. If cerebral thrombosis occurs in end vessels, as long contended in medical texts, the theoretical interest of this type of case is further enhanced. One of the authors' most interesting cases was that of an elderly lawyer who had experienced his accident in 1944, 2 years before he was first seen by them. His outstanding complaint concerned a central scotoma of the right eye, thought by his ophthalmologist to be on an arteriosclerotic basis. Before treatment he could distinguish a person standing 6 feet away but not his features; after 3 weeks of treatment he could differentiate all his major features.

The benefit that these patients experienced may have been strictly analogous to that seen in thrombosis elsewhere; or gliosis itself may have partially responded, as in Steinberg's cases of fibrositis and fascial contracture. Both Davison and Dowd suspect that some damaged nerve cells live in a twilight state, neither dead nor yet fully alive, until such a reparative stimulus as the tocopherols reach them and enable them to regain at least a portion of their former function. If every hypertensive were given tocopherols, would the incidence of apoplexy be reduced?

Discussion. The number of patients studied in each of these groups is small, but the results are of such interest, developed so promptly, and have such an important bearing on the great problem of heart and kidney disease that it was felt that they should be reported now.

Generally speaking, the tocopherols should be helpful wherever improved arteriolar circulation or better oxygen utilization in tissues is desired. It

would seem that when tocopherols are administered, thrombosed veins relax to permit a circulation over and past the thrombus, as Pereira has clearly shown can occur with sympathetic block in like cases.

The need for continued treatment at high dosage levels in so many cardiovascular conditions is analogous to the situation encountered in hormone substitution therapy, for example, as in hypothyroidism or in diabetes. It suggests that one is either replenishing a rapid wastage of tocopherols in these particular people or combatting the continued production of some noxious bodily antagonist. The authors' work with the purpuras would perhaps suggest the latter and may even point to that agent as being the estrogens - another indication of the truth of the thesis that vitamin E is anti-estrogenic, whatever else it is.

The matter of dosage is fundamental in tocopherol therapy. From about 200 to 300 milligrams of alpha tocopherol per day seems to be the average therapeutic level. The fact that it is alpha tocopherol that is required should be stressed. In cases of acute cerebral thrombosis the authors have used parenteral tocopherols with success. Patients so treated seem to react in from one half to one third of the usual time taken when tocopherols are administered by mouth. To achieve the best results in such cases it is important to saturate the patient as early as possible in order to minimize brain cell damage adjacent to the thrombus or embolus.

Inorganic iron should not be given with the tocopherols.

The authors hazard the guess that the tocopherols may be at least as valuable in the prophylaxis of certain vascular accidents and conditions as in the therapy. In this connection it should be pointed out that many of these conditions soon recurred after healing unless tocopherol therapy was continued at a high level permanently.

For too long, medical men have considered the vitamins to be mere food accessories. Surely the time is approaching when some of them, at least, will rank as true chemotherapeutic agents, to be administered in doses comparable to those of the sulfonamides or penicillin, and for indications quite as strict and clearly understood. (Surg., Gynec. and Obst., Jan. '48 - E. V. Shute et al.)

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Prevention of Experimental Arteritis in Dogs by Vitamin E: In a recent publication data were presented to show that the combination of a specified high fat diet and experimentally induced renal insufficiency in dogs is regularly followed by predictable lesions in the arterial system. The lesions have been found in elastic arteries, in muscular arteries, and in arterioles in practically every organ and tissue of the body with the exception of the kidney and liver. Essentially the lesion is an acute necrotizing arteritis of which the closest human counterparts are periarteritis nodosa and rheumatic arteritis.

When it was found that the dietary factor was lipid in nature, the question naturally arose concerning the effect of vitamin E, the so-called "fat antioxidant" vitamin, on these experimental arterial lesions, and a study on this question was made.

The methods for study, which have been detailed in previous publications, consist of feeding the dogs selected table scrap to which is added each day 3.0 c.c. per kg. of a commercial grade of cod liver oil. After this diet has been consumed for 8 weeks or longer, the kidneys are severely damaged by any one of several methods (heavy metal injury, bilateral nephrectomy, Leptospira Canicola - usually uranium nitrate, 10.0 mg. per kg. injected subcutaneously) and the arterial system is examined both grossly and histologically when the dogs die or are sacrificed days or weeks later.

In the first series of 4 dogs vitamin E (20 mg. of mixed natural tocopherols in one capsule) was given by mouth between 8 and 10 o'clock in the morning, and the dogs were fed the diet of table scrap and cod liver oil around 4 o'clock in the afternoon. Following kidney damage the dogs usually stopped eating on from the fourth to seventh day. Administration of vitamin E capsules was continued until the dogs died.

In the second series of 4 dogs vitamin E (in the same form as above) was not started until after the kidneys were damaged. The dogs were fed table scrap and cod liver oil for 8 weeks or longer, then a lethal dose of uranium nitrate was injected, and a single capsule of 20 mg. mixed natural tocopherols per day by mouth was started 0, 24, 48, and 72 hours after the heavy metal injury. Vitamin-E therapy was continued until the dogs died in uremia.

In these 8 dogs the single capsule of 20 mg. of mixed natural tocopherols amounted to from 2.5 to 4.0 mg. per kg. per day.

None of the 4 dogs fed vitamin E concomitantly with the specified high fat diet for 8 weeks or longer before kidney damage was induced developed arterial lesions. Of the 4 dogs in which vitamin E was started 0, 1, 2, and 3 days after renal insufficiency was produced, 3 did not develop arterial lesions; in the fourth, however, a lesion was discovered in routine histological section. There is a striking difference in the incidence of arterial lesions in these two groups as compared with similar experiments in which vitamin E was not administered. In one such experiment 22 of 25 dogs fed by the same method exhibited typical arterial lesions when they died in uremia from 7 to 35 days after the experimental production of renal insufficiency.

Since the pathogenesis of the arterial lesions related to high fat diet and renal insufficiency is not understood, there is no ready explanation for the protective action of vitamin E. The problem might be approached indirectly. If it is assumed that vitamin E exerts its usual "antioxidant" action, pathogenesis can be postulated as follows:

During the 8 weeks or more of dietary feeding, one or more of the "toxic" substances (fatty acids are under suspicion) contained in the diet saturates the tissues with the excess spilling over in the urine. When this safety valve is destroyed, the excess piles up to "explosive" levels, and the arterial lesions ensue. If the theory that the toxic substance is fatty acid proves correct, a corollary of it would be that the fatty acid damages collagen, for the first detectable anatomical change is edema, swelling, fragmentation, and necrosis of collagen. The subsequent fibrin, "fibrinoid," and intense leukocytic reactions that are seen in the typical arterial lesion presumably represent the response of the body to the necrotic collagen. Why the assumed fatty acid selects collagen in certain sites of the body for this activity, and whether it acts directly on the collagen in these sites or does so by inactivating vitamin C (which it has been shown to do in aqueous solutions in vitro) are not known. Attempts thus far to demonstrate any variations in ketone bodies in the urine or any consistent variations in the blood plasma lipids at different stages in the experimental procedures have not yielded definite confirmatory evidence for the above hypothesis. (Proc. Soc. Exper. Biol. and Med., Nov. '47 - R. L. Holman)

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Influence of Alpha Tocopherol on Implantation in Old Rats: Investigations concerned with the fertility of female rats on vitamin E-deficient diets have been mainly focused on the "resorption gestation." The question of implantation in vitamin-E deficiency has received much less attention.

In this study the implantation rate in female rats on a purified diet containing about from 1 to 4 mg. of tocopherols per 100-Gm. diet was compared with the implantation rates in animals on the same diet receiving single and continuous supplements of synthetic dl alpha tocopherol acetate. Failure of implantation was observed after the eighth month in females without tocopherol supplements. With continuous tocopherol administration, the implantation rate was normal after one year. Single tocopherol supplements postmating increased the implantation rate in older rats significantly. The requirements necessary for successful implantation in older rats vary widely and increase steeply with age.

Infections of the uterus and the tubes were frequently observed in the E-deficient rats, but not in those on the complete diet. The presence of infection does not explain the higher implantation rate after single tocopherol doses postmating.

The changes leading to the failure of implantation are prevented by alpha tocopherol acetate, but once present, are only partly counteracted by its administration. (Proc. Soc. Exper. Biol. and Med., Nov. '47 - H. Kaunitz and C. A. Slanetz)

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Interrelation Between Alpha Tocopherol and Protein Metabolism: In a previous paper by Hove, one of the authors, in 1946, it was reported that d, alpha tocopherol reduced weight loss in adult rats maintained on a 5-percent crude-casein diet for extended periods of time. It was pointed out that this result was in apparent contradiction to the work of Dam who had noted, in 1944 no influence of alpha tocopherol on the body weight of rats maintained until death on a diet containing approximately 5-percent protein from yeast. It occurred to the authors that the 4-week, rat-growth method originated by Osborne, Mendel, and Ferry in 1919 for determining protein quality might be useful in resolving these divergent results.

The results from 5 consecutive experiments showed that:

When the casein level in the diet of young rats was between 6 and 12 per cent, d, alpha tocopherol increased the utilization of casein protein for their growth. However, there was no benefit due to tocopherol at casein levels over 12 per cent or under 6 per cent in the 4-week test period. The average protein-efficiency ratio for the control groups was 1.88, as compared with 2.18 for the tocopherol-supplemented groups. The beneficial effect of alpha tocopherol was as evident on equalized feeding as on ad libitum feeding technics. The incidence of stomach ulcers and the bleaching of maxillary incisors which occur in rats maintained on low-casein diets are reduced by d, alpha tocopherol. A yeast-protein concentrate or 0.1 per cent xanthine in the diet is as effective as alpha tocopherol in increasing the utilization of casein protein.

This effect of tocopherol in improving efficiency of food utilization has been noticed by Patrick and Morgan in chickens fed a synthetic diet containing casein protein. An explanation for the beneficial influence of tocopherol on food utilization efficiency or on protein-efficiency ratio may be found in an experiment described by Bosshardt et al. As non-protein calory intake increased, protein intake remaining constant, the protein-efficiency ratio was found to increase. Consequently, in the authors' experiments tocopherol may be increasing the efficiency of fat metabolism, thus giving, in effect, a higher calory intake and resulting indirectly in a higher protein-efficiency ratio.

The ability of alpha tocopherol or xanthine to improve casein utilization may be related to the observations in the work of Schwarz that these compounds prevented cirrhotic changes in the liver and death of rats on a diet containing 15-percent alkali-extracted casein. Traces of xanthine contained in crude casein would be removed by the alkali extraction and a xanthine-free diet would result. Giri and Rao reported that xanthine functions as an antioxidant in metal catalyzed oxidations, and it may be in this same capacity that it acts similarly and nonspecifically with alpha tocopherol in vivo.

Schwarz found dried yeast, 0.5 Gm. daily, to be but slightly active, but results of the authors showed a yeast protein concentrate to be highly active. The active agent in the yeast preparation used by the authors may have been liberated or formed from precursors during the enzymatic digestion. Studies

on this problem as well as the influence of other purine bodies and of folic acid are being pursued. In this regard Bosshardt et al., in working with mice, noted an increased utilization of casein protein produced by a butanol extract of liver.

As mentioned before, tocopherol did not increase the protein-efficiency ratio in rats on diets with casein levels as low as 5 or 6 per cent, over the 4-week test period. In a previous experiment, however, rats kept on such diets for periods up to 20 weeks showed a dramatic growth and survival benefit from alpha tocopherol. This difference may indicate that the interrelation between protein and alpha tocopherol follows separate and independent mechanisms under these 2 experimental conditions. (J. Nutrition, 10 Nov '47 - E. L. Hove and P. L. Harris)

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The Effect of Adrenal Cortical Substances on the Central Nervous System: Previous investigation, by one of the authors, of cerebral lesions which follow arrest of the cephalic circulation revealed a very striking picture of edema and changes in cell and vessel membranes with highly localized destruction. Two possible mechanisms of injury were suggested: (a) disturbance of the blood-brain barrier with permeability changes and shifts in electrolyte balance; and (b) possible interference with local enzyme systems primarily involving one or more of the intermediary steps in carbohydrate metabolism. Consideration of these two mechanisms immediately focused attention on the possibility that the adrenal cortex might play a role of major importance in the protection of the central nervous system from such damage, because various fractions of the adrenal cortical hormone are known to influence both electrolyte balance and carbohydrate metabolism.

Two groups of experiments were performed. The first group was designed to test the possible influence of adrenal hormones on relatively mild injury - injury in the form of exposure edema. Three criteria were used as indices of the anatomic and functional status of the brain tissue: (a) the electroencephalogram as a measure or correlate of function; (b) reaction to injection of 1-percent trypan blue as an indication of integrity of the blood-brain barrier, and (c) microscopic sections for changes in morphology. The second group of experiments was set up to determine the effect of the adrenal substances on the electroencephalogram of the control (not operated upon) animals. Cats, rabbits, rats, and man (in two experiments) were used. The procedure was carried out on unanesthetized and curarized animals, as well as on animals anesthetized with pentobarbital sodium, urethane-ether, chloralose, "evipal" and "dial." Each experiment was carried out in duplicate, except for the titration experiments which were carried out on 6 cats.

The preoperative record of the animal given intramuscular injection of total extract 1 hour before exposure demonstrates markedly greater amplitude and faster frequency than that of the control.

It was seen that in the untreated animal complete flattening of the brain waves appeared 3 hours following operation; even 24 hours later the record was still abnormal. However, no significant abnormality was seen in the electroencephalogram of the adrenal treated animal 3 hours after exposure, nor did it show any of the slow frequency seen in the control 24 hours later. Both animals received two injections of 10 c.c. per kg. of 1-percent trypan blue into the saphenous vein; one 3 hours after exposure, and another just prior to removal of the brain for sectioning. (In the normal animal, trypan blue fails to stain the central nervous system - i.e., does not pass the blood-brain barrier - except for the tuber cinereum and region of the chiasm, the pituitary, the choroid plexuses and the area postrema.) On gross examination, the brain of the untreated animal showed marked blue staining extending into the white matter at the area of exposure. The adrenal treated brains showed no staining in some cases; in others a much less extensive area of faint staining was evident. In some cases, the staining reaction was somewhat equivocal, but in no case did the staining in the treated animals approach the intensity observed in the controls. Two associated points are to be noted. First, during the course of the experiments, gross edema was observed only in the controls, evidenced by bulging of the brain substance through the trephine hole in the calvarium, accompanied by disappearance of the brain pulsations. Secondly, examination of thionin-stained sections revealed the presence of marked intra- and intercellular edema in the controls, a pathologic picture that was absent following injection of the adrenal cortical extract.

It was pointed out that in the preoperative post-injection record of the treated animal, marked changes could be observed in contrast to the preoperative tracing in the control. The observation that the hormone appeared to influence the electrical activity of the brain in the intact (not operated upon) animal attracted immediate attention. Consequently, the electroencephalogram of a normal animal was recorded following pentobarbital anesthesia. Twenty-one minutes after the injection of 2 c.c. per kg. of aqueous adrenal cortical extract, marked changes in amplitude were obvious; the increase in voltage was carried still further 32 and 50 minutes post-injection. This procedure was carried out in a series of animals in all of which similar changes in amplitude and frequency were observed.

However, there remained the possibility that these effects were in some way related to the anesthesia - in other words, that there might be some combined action of the hormone with pentobarbital. For this reason, both lipoadrenal cortical hormone (Upjohn) and aqueous adrenal cortical hormone were injected intramuscularly and intravenously in the unanesthetized animal and man, as well as in the curarized animal, and in animals anesthetized with urethane-ether, "evipal," chloralose, and "dial." The results already obtained were confirmed by these experiments. In man only one experiment has been carried out thus far, in which incipient changes in amplitude and frequency (of the same nature as those seen in the experimental animals) appeared following the intravenous injection of 0.5 c.c. per kg. of aqueous adrenal cortical extract. The changes, in both animals and man, appeared from 5 to 10 minutes

after intravenous injection, and from 20 to 30 minutes after intramuscular injection. The minimal effective dose and time of latency of the recorded reaction remained to be determined. This was done by the intravenous injection of 0.25 c.c. per kg. doses at 8 minute intervals.

With this procedure, it was observed that definite changes appeared in the electroencephalogram 8 minutes after a total of 0.5 c.c. per kg. had been injected. These changes progressed following doses of from 1 to 2 c.c. per kg., at which point an asymptote was reached. No further increase in amplitude or frequency could be produced with greater amounts of the hormone. In extremely large doses the bursts of marked activity in the electroencephalogram alternate with periods of depression. In one animal which was given up to approximately 20 c.c. per kg. of the hormone, the bursts of enhanced voltage still appeared at intervals.

The question arose concerning whether or not individual fractions of the total cortical hormone could produce or were producing the observed reaction. The first attempt to answer this question was the injection of desoxycorticosterone acetate. It appears that the DCA produces the same type of increase in amplitude as that brought about by the total adrenal hormone itself, but the frequency changes are apparently not of a like nature. If anything, the enhanced amplitude following DCA was accompanied by slow frequency in contrast to the fast frequencies seen after injection of total extract. Further experiments with DCA and other similar compounds remain to be performed.

In the light of present knowledge, there can be little question of the validity of the thesis that the adrenal glands profoundly influence resistance and defense mechanisms of the body. There is an ever increasing mass of clinical and experimental data serving to point out and attempting to explain changes in the adrenal cortex following poisons and infections and in conditions of stress or shock, as well as the role of the cortical hormones in the formation of antibodies and other physiological events. Evidence has been obtained demonstrating that the adrenal cortex is related to carbohydrate metabolism, to salt and water metabolism, to utilization of certain of the vitamins, and is intimately concerned with processes of tissue respiration. Perla and Marmorston summarize these relationships in the following statement:

"It would seem probable that the mechanism of natural resistance is dependent on the maintenance of normal cellular metabolism and that procedures that impair oxidation and reduction processes depress the resistance of the somatic cells to all abnormal stimuli, whether marked variations in temperature or poisons, toxins or infectious agents. When the physiologic action of the cortical hormone is better understood, the exact chemical nature of the life-prolonging hormone identified, and its relation to oxidation-reduction systems determined, a new approach to the problem of the mechanism of natural resistance in the body may be available."

Following this line of reasoning, the authors instituted a course of injections of adrenal cortical hormone in a case of post-traumatic concussion

syndrome in man (about one month after injury). The results have indicated that further clinical and experimental investigations of this problem should be carried out. Using a minimum dose of 20 c.c. of aqueous extract per day (from the findings the authors now suggest a level of at least 0.5 c.c. per kilo per day) it was noted that by the third day of this therapy the incessant headache had disappeared. An electroencephalogram taken 2 weeks after treatment was begun showed no abnormality whatsoever - the slowing and irregularity seen 1 month before was no longer in evidence. The patient has been followed up to the present time and has shown no recurrence of any of the symptoms. Other problems relative to these findings will be discussed below. An indication of confirmation of these results is suggested in the report of Aird:

"Neurophysiological studies on cerebral concussion have demonstrated that the permeability of the blood-brain barrier is increased after concussion and that this effect persists...in apparent association with the post-concussional dysrhythmia observed electroencephalographically....When measures were taken to decrease the permeability of the blood-brain barrier..., these effects...could be prevented in large part....Preliminary clinical studies, which are at present under way, suggest that adrenal cortical extracts...may have some beneficial effects on the post-concussional state."

In Addison's disease patients tend to show symptoms of insomnia, restlessness, abnormal sensory reactions, apathy, anxiety, fatigability and general ineffectiveness--a picture described as subacute adrenal deficiency. These symptoms may precede or occasionally overshadow other clinical symptoms or biochemical findings to such an extent that the patient is sent to a psychiatric service. Improvements in vision, insomnia, fatigue and tremor occur with adequate adrenal cortical extract therapy. Engel and Romano reported abnormal electroencephalograms in Addison's disease during all stages of therapy. The records were most abnormal during the crisis, showing marked slowing with an average frequency of about 7 per second. With adequate adrenal cortical treatment (100 c.c. over 5 days) the electroencephalogram returned to normal, showing an average frequency of from 9 to 10 per second. Other reports of the ineffectiveness of cortical extract in such cases appear to have been due to low, inadequate dosage.

Engel and Romano also found that desoxycorticosterone acetate would only partially restore the electroencephalogram. From the authors' findings thus far it seems that desoxycorticosterone has more effect on amplitude than on frequency. It may be that both electrolyte balance and carbohydrate metabolism must be affected in order to produce the complete result. Later experiments may afford the answer to this question.

A further point of interest relative to the picture in Addison's disease, is the increased susceptibility and sensitivity to drugs. The patient is unusually sensitive to narcotics such as morphine and codeine, and to sedatives, including paraldehyde, bromides, and barbiturates. Coma and respiratory failure may

follow administration of the usual therapeutic doses of these compounds. Restoration of adrenal cortical levels overcomes this susceptibility to drugs depressant to the central nervous system.

In bilaterally adrenalectomized rats as in the Addisonian patient, there is fatigue and a disinclination for exercise. The animals lose interest in their surroundings, and at times may become almost comatose. In some cases they become easily irritated or disoriented. The reflexes of these animals are more easily fatigued than the normal. The resistance to the reflex fatigue may be increased as much as sixfold following adrenal cortical administration according to Hartman, Beck and Thorn. Furthermore, Liddell has observed that adrenal cortical extract exerted a marked ameliorative influence on the manifestations of "experimental neurosis" in sheep.

It appears then that adrenal cortical extract exerts a profound effect on the central nervous system, which is reflected to some extent, at least, in the activity of the brain as measured by the electroencephalograph. Part of this influence may be transmitted through a metabolic mechanism, but unquestionably a large part is manifested as a control or regulation or preservation of the blood-brain barrier and its permeability. The authors' experiments with the hormone in cases of exposure edema have definitely confirmed those of Prados, Strowger, and Feindel who first reported the efficiency of these glandular preparations in preventing leakage of trypan blue through capillary walls after exposure. They observed that, "...as a result of exposure the capillary endothelium becomes more permeable. This allows not only an increased outflow of fluid into the interstitial spaces, but the leakage of substances which in normal conditions are not permeable through the so-called blood-brain barrier." There is considerable evidence in the literature that adrenal hormones influence capillary permeability, and that the capillaries of the adrenalectomized animal are dilated and abnormally permeable. The edema which can follow such abnormality, and which has been seen after arrest of cephalic circulation, concussion, exposure, etc., should, therefore, be affected by adrenal extracts. The experiments performed by the authors would suggest that such, in fact, is the case.

It is possible that the electroencephalographic findings may also be of value in relation to the problem of the origin of the electroencephalogram itself. The present observations, plus results of experiments in progress, should lead to at least one more correlate of nervous system activity and its reflection in the electroencephalogram. If adrenal hormones cause neurones to fire in some specific way, there should be the possibility at hand of localizing some of the basic physiological factors underlying electroencephalographic activity.

It is felt that the results of these studies have important physiological and clinical implications. (J. Neurosurg., Nov. '47 - R. G. Grenell and E. L. McCawley)

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Ascorbic Acid, Thiamine, Riboflavin and Niacin in Relation to Acute Burns in Man: Alterations in the metabolism of proteins, carbohydrates, and electrolytes following burns have been extensively studied in the past few years, but few investigations of possible changes in vitamin metabolism following burns have been made. Uzbekov, Clark, and Rossiter and Harkins have reported decreased ascorbic acid content of the adrenal cortex in burned guinea pigs and rabbits, and Lam has reported a decrease in the plasma ascorbic acid concentration in patients with extreme burns. Andreae, Schenker, and Browne found that patients with burns or fractures characteristically showed a pronounced retention of riboflavin during from three to 5 days after injury. This was followed by a period of similar duration in which there occurred an increased loss of riboflavin in the urine. About 10 days after injury the riboflavin balance returned to normal. They suggested that the riboflavin retained during the first period was stored in some way and subsequently released. Later, during the convalescent period, both nitrogen and riboflavin were retained, 0.3 mg. of riboflavin being retained for each gram of nitrogen. Andreae and Browne, in a later report, confirmed these observations, and in addition reported a high retention of ascorbic acid in similar patients in the early days after injury, which, in contradistinction to the retention of riboflavin, was not followed by a period of increased loss of ascorbic acid. This, they expressed the belief, could not be attributed to pre-existing deficiency, faulty absorption, impaired excretion, retention in the tissues or in the edema fluid, or excretion in the form of dehydroascorbic acid.

The present study is concerned with the alteration in the plasma concentration of ascorbic acid and in the urinary excretion of ascorbic acid, thiamine, riboflavin, and N-methylniacinamide in patients with burns admitted to the Boston City Hospital during 1944-1945.

It was found that after severe burns there are considerable alterations in the metabolism of ascorbic acid, thiamine, riboflavin, and niacinamide, as evidenced by a low concentration of ascorbic acid in the plasma either with the patient fasting or after saturation tests and low urinary excretion of these vitamins either with the patient fasting or after the injection of test doses. The extent of the abnormalities paralleled the severity of the burn. Patients with burns, minor in extent and superficial in depth, did not show these changes unless there was in addition some complicating factor such as pre-existing deficiency, low intake of food, or serious infection. In contrast, patients with extensive deep burns invariably showed notable abnormalities. These changes were greatest in the early period following injury but continued in some cases far into the chronic stage. In this respect, the upset in vitamin metabolism parallels the upset in nitrogen metabolism which follows burns.

The following factors must be considered in an attempt to account for the findings.

1. Pre-existing Deficiency. Three patients gave evidence on entry to the hospital of possible vitamin deficiency. One was a previously healthy young

woman whose diet was adequate except for lack of citrus fruits. There were no stigmas of ascorbic acid deficiency on admission. Her burn was minor. She remained on a diet low in vitamin C for six weeks, and during this time the fasting hourly excretion rate of ascorbic acid and the fasting plasma ascorbic acid concentrations were low. The excretion of the other vitamins was normal. A skin graft at this time failed. Thereafter she received a supplement of 1 Gm. of ascorbic acid daily, and the plasma vitamin C level and the urinary excretion rose to normal. A skin graft at this time was completely successful. Another patient who entered the hospital with probable pre-existing vitamin deficiency was a 60-year old man who for a period of six months prior to entry ingested a poor diet and large quantities of alcohol and suffered from intermittent bloody diarrhea. On entry to the hospital he was moderately underweight, but there were no definite stigmas of specific vitamin deficiency. His burn was of moderate severity. During the first week, the urinary excretions of thiamine, riboflavin, and n-methylniacinamide were low (excretion of ascorbic acid not measured), and the fasting plasma ascorbic acid levels were also low. Thereafter he was given large daily supplements of all vitamins, and the urinary excretions of the four vitamins and the plasma ascorbic acid concentration rose to normal levels. The third patient who entered the hospital with probable pre-existing nutritional deficiencies, although none were apparent on entry, was a 27-year old man who had been an alcoholic for the year previous to injury. Despite a daily supplement of 750 mg. of ascorbic acid daily, chiefly by the intramuscular route, his plasma ascorbic acid concentration fell to zero in the second week and remained at this level even after 4 Gm. of ascorbic acid had been given in two days. This would indicate that some factor in addition to possible pre-existing deficiency was present in this patient, since the experiments of Crandon, Lund, and Dill showed a much more rapid rise in the plasma ascorbic acid after actual scurvy had been treated with comparable amounts of vitamin C. In the other cases studied pre-existing deficiency did not play an important role.

2. Inadequate Dosage. In a few patients the intake of the various vitamins was probably low and may have accounted in part for the finding of low excretion values. However, in the patients with the most pronounced abnormalities the actual intake of vitamins was extremely high - far above the so-called optimum amount for healthy persons.

3. Failure of Absorption. Failure of absorption can be ruled out by the fact that in the most severely burned patients, who showed the most striking changes, the vitamins were given slowly by intravenous or intramuscular routes.

4. Excretion in Sweat. Sargent, Robinson, and Johnson have shown that significant quantities of these vitamins are not lost by this route even under conditions of extreme sweating.

5. Excretion in Edema Fluid or into the Exudate from the Burned Surfaces. Andreae and Browne have shown that the concentration of ascorbic acid in the early edema fluid of burns is similar to the concentration in the blood plasma. They expressed the opinion that diversion of ascorbic acid into the edema fluid cannot account for the changes observed in the metabolism of ascorbic acid. The amounts of other vitamins excreted in the early edema fluid or of all the vitamins excreted in the later exudate have not been determined. However, the excretion in the exudate cannot explain the early findings, because during the first week the external exudation from deep burns is minimal, and it is the patients with deep burns who demonstrate the most appreciable changes. On the other hand, it may account in part for the findings in the later stages of the injury.

6. Storage. Andreae and his associates interpreted the evidence from their studies as indicating that riboflavin is stored early after injury and excreted later, but in the case of ascorbic acid there is no evidence for storage, since the early "retention" was not followed by a period of increased excretion. There are no data in the present study which would suggest an early storage, but it is possible that such could not be demonstrated by the technics used.

7. Excretion of the Vitamins in Forms Other Than Those Measured. Thiamine and niacinamide are excreted in a multiplicity of forms, and it is possible that determinations of the excretion of only one of the forms does not give a true picture in the case of these vitamins. Ascorbic acid is excreted in normal persons chiefly in the reduced form, but a small proportion is excreted in the reversibly oxidized or dehydro form. Andreae and Browne found no disproportionate amount of dehydroascorbic acid in the urine of burned patients. On the other hand, an increased proportion of dehydroascorbic acid has been reported in the adrenals of burned animals. Whether ascorbic acid may be excreted in other forms, such as the irreversibly oxidized form, is not known. Riboflavin, as far as is known, is excreted as such.

8. Destruction. It is possible that the vitamins may be destroyed in the burned patients without any useful function being performed during their destruction. This study contributes no evidence for or against such a postulate.

9. Increased Utilization. It has been shown in recent years that many of the vitamins play more fundamental roles than merely the prevention or curing of the well known deficiency syndromes such as scurvy, beri-beri, and pellagra. Thiamine, riboflavin, and niacin are concerned with the enzyme systems that control carbohydrate metabolism, and in addition riboflavin is important in amino acid metabolism. Ascorbic acid has been shown to have a fundamental role in the formation of the adrenocortical hormone and in general tissue metabolism. These functions indicate that the four vitamins play important roles in connection with recovery from hemorrhagic shock, injury and acute infections, since disturbances in the metabolism of carbohydrate, protein, and adrenocortical hormones are found in these conditions. Thus, Govier has

found that the mortality of normal dogs exposed to a standardized type of hemorrhagic shock was reduced when thiamine was given in large doses before or after bleeding. In addition, dogs deficient in thiamine were particularly susceptible to death from hemorrhagic shock. Holt has demonstrated apparent increased utilization of thiamine in conditions of stress such as increased basal metabolism and fever. On the other hand, Bergman and others were unable to show any beneficial effect of thiamine or ascorbic acid used alone as sole therapeutic measures in the treatment of shock due to scalding burns in mice. In the later period of burns, when epithelization and formation of granulation tissue are taking place, it is probable that there is an increased demand for ascorbic acid and riboflavin and possibly for other vitamins.

Summary and Conclusions. The results from this study should be considered to indicate, as a first approximation, that large doses of ascorbic acid, thiamine, riboflavin, and niacinamide are needed by severely burned patients and that supplementation at a lower level is needed for many patients with burns of moderate extent. A similar conclusion has been reached in a study of patients with hemorrhagic shock, traumatic injuries, and infection.

It is suggested that from 1 to 2 Gm. of ascorbic acid, from 10 to 20 mg. each of thiamine and riboflavin, and from 150 to 250 mg. of niacin be given daily to severely burned patients and that the doses may be needed for long periods. However, these vitamins alone will not satisfy the nutritional needs of the patient, which include a high protein, high carbohydrate diet and ample quantities of yeast, crude liver extract (given orally), and vitamins A and D. (Arch. Surg., Nov. '47 - C. C. Lund et al.)

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Relation Between Thiamine and Arsenical Toxicity: Intensive arsenotherapy has been used extensively since 1939, but with constant apprehension because of the increased danger of cerebral complications. Thomas and Wexler stated that the incidence of cerebral symptoms was about 1 per cent in all quick methods of treatment.

Many conflicting theories of arsenical encephalopathy are recorded in the literature, the confusion being manifested in the variety of names given to the syndrome: "hemorrhagic encephalitis," "brain purpura," "serous apoplexy," "medullary perivascular necroses," and "pericapillary encephalorrhagia." The cause of the syndrome has been variously attributed to: (a) the liberation of trivalent inorganic arsenic, due to faulty elimination of the drug by the kidneys and accompanying uremia, (b) a Herxheimer reaction, (c) anaphylaxis and allergy, (d) syphilis itself, (e) injury to the endothelium by a toxin or infectious process, causing hypervascular dilatation and involvement of the nutrient blood vessels, (f) primary cellular damage of brain tissue with accompanying edema, softening and necroses, (g) hepatic dysfunction and vitamin B_1 deficiency, and (h) interference with cellular function by the arsenical combination with the enzyme proteins, physiologically essential groups in the cell,

specifically of cellular sulfhydryl (SH) groups associated with enzyme proteins.

Of all these theories, the last-mentioned more nearly explains the rapid intoxication which may follow arsenical therapy. Most of the other theories were propounded by pathologists to explain merely the pathologic process. Until recently, successful treatment had not been introduced for this syndrome. However, the introduction of 2,3-dimercaptopropanol (BAL) by Peters, Stocken, and Thompson and its subsequent clinical utilization have apparently reduced the mortality rate.

The authors' interest in this study was stimulated in 1943 by the rapid recovery, after parenteral administration of massive doses of thiamine hydrochloride, of a patient in Victoria Hospital in whom peripheral neuritis and suspected arsenical encephalopathy had developed during the course of the 5-day drip treatment. The literature revealed that vitamin B_1 might be a factor in this syndrome, and an extensive survey showed that there was an amazing similarity between the manifestations of arsenical encephalopathy and acute vitamin B_1 deficiency.

Ferraro stressed the organ immunity from sensitivity to a particular toxin. Also, there is a direct relation between the intensity of reaction and the degree of concentration of the toxic substance. Changes in the brain similar to those noticed in arsenical encephalopathy are known to occur in vascular damage, provoked by a variety of dissimilar poisons (such as carbon monoxide, phosgene, and mercury) and by anoxia. The poisons mentioned produce direct or indirect anoxia. Since the brain is especially susceptible to anoxia from any cause and so dependent for energy on efficient carbohydrate metabolism, it is not impossible that this cerebral syndrome may be caused by enzymatic dysfunction. The work of Peters, Stocken, and Thompson revealing the arsenical combination with the protein enzyme action of the tissue cell structure, thus interfering with function, might well bear this out. In addition, the fact that Wernicke's syndrome, the end picture of acute B_1 avitaminosis, so closely parallels arsenical encephalopathy directs attention to cocarboxylase.

Comparison of these two syndromes and the fact that peripheral neuritis is described as a not infrequent reaction to the 5-day drip led to the supposition that arsenical encephalopathy and acute vitamin B_1 deficiency have a common causation. A review of the role of thiamine in carbohydrate metabolism suggested that a study of patients undergoing intensive arsenical (5-day drip) therapy for early syphilis might shed some further light on this important deduction. Such a study might determine whether the patient was primarily deficient in vitamin B_1 or was rendered deficient by arsenical administration, and might determine the prophylactic or curative value of thiamine in reducing the cerebral complications due to arsenicals. Sherman and Elvehjem finally proved that vitamin B_1, in the form of diphosphate ester, is needed for the

oxidative removal of pyruvic acid and indirectly of lactic acid. Extensive investigation has shown that both lactic acid and pyruvic acids accumulate in the blood and tissues, and the pyruvic acid and other alpha-keto acids are excreted in increased amounts in the urine during the period of thiamine deficiency.

Levels of thiamine in the blood do not give a reliable estimation of the amount of diphosphothiamine functioning as the co-enzyme in the tissues. Therefore, following the methods of Stotz and Bessey, the authors used the ratio of lactate to pyruvate in the blood to estimate the level of vitamin B_1. This ratio takes into account all variables, such as anoxia from injections of dextrose and exercise. For every given level of lactic acid there is an associated level of pyruvic acid. If the level of pyruvic acid is higher than that given by the ratio, then that excess measures the state of deficiency.

Experiments showed that oxophenarsine hydrochloride does cause a significant derangement in carbohydrate metabolism, as evinced by increased pyruvic acid and sugar in the blood. The greater the clinical toxicity, the greater is the upset of carbohydrate metabolism. The high level of pyruvic acid suggests that catabolism is stopped at the level of pyruvic acid. This is directly related to the functioning level of thiamine, since a deficiency of the co-enzyme containing thiamine produces a high level of pyruvic acid.

A sudden rise in the level of pyruvic acid, coinciding with greatly increased muscular sensitivity and rising temperature, is experimental evidence of a reaction of severe toxicity. In a reaction seriously involving the central nervous system, if vitamin B_1 and 2,3-dimercaptopropanol (BAL) are to be used therapeutically, they must be given early, before the reaction has gone beyond the irreversible pathologic lesion.

In 5 cases of acute arsenical intoxication the level of pyruvic acid was high throughout the course of the oxophenarsine hydrochloride drip, and the curves portraying this high level of pyruvic acid were all of the same general shape. It would seem that BAL and vitamin B_1 in adequate dosage should be complementary in the treatment of arsenical encephalopathy. Administration of vitamin B_1 insures the functioning at peak levels of the cell enzyme systems not affected by the arsenical. When the usefulness of vitamin B_1 has been exceeded, then BAL may be used to inactivate the arsenical, though, of course, this means the loss of its spirocheticidal effect. Lastly, an initial pretreatment high level of pyruvic acid accompanied with clinical signs of subacute B_1 avitaminosis should warrant the use of treatment other than intensive arsenotherapy. (Arch. Dermat. and Syph., Nov. '47 - G. B. Sexton and C. W. Gowdey)

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Ascorbic Acid in the Treatment and Prevention of Poison Oak Dermatitis: The study of dermatitis venenata due to varieties of poison oak was undertaken with the assumption that the manifestations observed in the disease were probably due, as in other allergic states, to an overproduction of histamine and other

such monoamines in the body tissues. The hypothesis was carried still further, based on the probability that the irritating factor, a volatile oil, first decomposes the protein molecules in the cutaneous tissues into a-amino acids by a process similar to that of the proteolytic enzymes in digestion. These amino acids may further be decomposed not according to the normal method of deamination and oxidation but by losing carbon dioxide from the carboxyl group (decarboxylation) with the formation of a corresponding alkyl amine, as:

$$R\text{-}CH(NH_2)\ COOH \xrightarrow{-\ CO_2} R\text{-}CH_2NH_2$$

Various studies have shown that the monoamines, such as tyramine and histamine, have a powerful physiologic action even in minute quantities. Histamine, when injected into the body, promptly causes increased arterial tension, and later, a fall in blood pressure results from increasing capillary permeability. This would probably explain the hyperemia seen in early manifestations of poison oak dermatitis and the subsequent vesiculation of the cutaneous tissue.

Because one of the physiologic actions of ascorbic acid is involved in the maintenance of tissue integrity and because integrity of the vascular endothelium is of particular importance, it was conceived that ascorbic acid in increased amounts might counteract the toxic actions of alkyl amines like histamine. An experimental study carried out by the author on rabbits proved this to be true. With this in mind and the knowledge of the harmless effect of ascorbic acid on the human body, a study of the treatment and prevention of poison oak dermatitis by ascorbic acid was undertaken.

Three hundred and eighty patients with dermatitis venenata due to poison oak were observed and treated by the author and associates. Of these, 126 received treatment with ascorbic acid, and the results were favorable, with some startlingly so. The average period of treatment for the 126 patients was 5 days, the shortest 2 days, and the longest 10 days. It was noted that the earlier treatment was initiated after exposure the quicker and more favorable was the recovery. The ascorbic acid was given only to those patients who presented manifestations of moderately severe or severe disease. The best results were usually obtained in those persons who presented edema, as of the eyelids and genitals. Patients with mild dermatitis were treated with the usual topical application of calamine lotion or tincture of ferric chloride.

Most of the patients treated were ambulant. Only a few with severe dermatitis had to be hospitalized, and hospitalization in these cases was primarily due to the unavailability of ascorbic acid at one time or another.

Sterile ampules of ascorbic acid solution, 100 mg. each, were employed two or three times a day at intervals of from 4 to 6 hours. Although the dosage varied somewhat and depended on the severity of the dermatitis, it is felt that the maximum daily dosage required in any case is 600 mg. of ascorbic acid. However, it may be given up to 1 gram or more daily. It is believed that a more concentrated

solution or a preparation of a water-in-oil emulsion of ascorbic acid to effect a prolonged action would serve the purpose more satisfactorily. The best route of injection seems to be the intramuscular one, for, if given intravenously, the ascorbic acid is eliminated too rapidly from the blood stream. The subcutaneous method is too painful. It is also advisable under certain conditions to give the ascorbic acid in tablet form by mouth to supplement that injected. When ascorbic acid is given orally, twice the amount that is employed by injection should be given. This, however, does not completely replace the injections. When vesiculation is present topical application of calamine lotion is recommended as a supportive measure.

At no time were deleterious effects from the drug observed. In fact, patients usually said that they felt well while taking the ascorbic acid. After starting treatment the first sign of improvement is a reduction in itching which may be noticed in about from two to four hours after the first injection. This improvement wears off in a few hours if no further ascorbic acid is given. That is probably due to the fact that the ascorbic acid is rapidly eliminated from the system.

In the determination of prophylaxis against poison oak dermatitis, two groups of men (24 in each group) who were sensitive to the plant were tested. Each group was divided into two sections, 12 men in each section. During the period of exposure to poison oak, those in one section took the prescribed prophylactic dose of ascorbic acid and those in the other did not. Those who took the prophylactic dose of ascorbic acid did not contract the disease when exposed, but a large percentage of those who were not given the daily dose of ascorbic acid did contract poison oak dermatitis, ranging from mild to severe. The dose which is felt to be adequate for protection ranges from 150 to 300 mg. daily and can be taken in tablet form in divided doses. This daily dose must be taken one day prior to exposure, every day during exposure, and at least from 24 to 48 hours after exposure.

Despite the small number of patients treated and the diverse intensity of the reactions of different persons susceptible to the poison of Toxicodendron and to treatment, which make it difficult for reaching concise conclusions, it is nevertheless felt that ascorbic acid is an effective therapeutic agent and has definite possibilities as a preventive. (Arch. Dermat. and Syph., Dec. '47 - D. H. Klasson)

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Removal of Fluorides from Water: Fluorides in drinking water can be beneficial or detrimental depending on their concentration. Recent epidemiological studies have indicated that there is an inverse relationship between fluorides ingested and the incidence of dental caries. The promise which this relationship holds for mass control of dental decay, however, hinges on the fact that an optimal prophylactic effect of the fluoride against caries is obtained within the range of from 1.0 to 1.5 parts per million. Greater concentrations are associated with a hypoplasia of the teeth known as mottled enamel or dental fluorosis.

More than a million persons in over 500 communities in the United States are now using public water supplies containing in excess of 1.5 p.p.m. fluorides. The disfiguring dental condition which is caused by the use of such waters for drinking purposes can be prevented in future populations of these communities by removing the excess fluorides from the communal water supplies. However, most of the removal processes now available appear to be either too expensive to operate or too complicated for routine application by the average operator of a small water-treatment plant. There is an urgent need for the development of a process comparable in operating costs and simplicity to the lime-soda ash softening process.

The problem of choosing the most practical method of defluorination for a particular supply is difficult, because of the almost complete absence of operational data. The choice of method for the accomplishment of a similar purpose as in other treatment processes depends on the rate of water consumption and on the characteristics of the raw water. For large municipal plants which treat waters requiring a reduction in hardness, it is advisable, in general, to reduce the fluorides as much as possible by the lime-softening process. In some cases it would be economical to balance the costs of pre-carbonation and sludge disposal against the addition of a limited quantity of magnesium compounds. Excess fluorides remaining after this process could be removed in gravity contact filters or by an aluminum-clay floc, with subsequent separation of the floc from the water.

In small plants where softening is not desired, pressure contact filters appear to be more economical. Where the water is hard, lime softening is indicated up to a raw-water fluoride content of about 4.0 p.p.m. If the fluoride exceeds this figure in hard waters, the remaining fluorides can be removed by contact filters.

The tricalcium phosphates and the resinous ion exchangers, when used in contact filters, appear to have the highest exchange capacities for fluorides. Furthermore, the chemical cost for regeneration of these materials is relatively economical.

Because the current knowledge of the chemical processes involved in removal of fluorides is very limited, additional fundamental research in this field is needed. Further, the practical usefulness of the available methods and those now undeveloped must be tested on a pilot plant scale, and their relative worth under varying conditions must be determined. Until this information is available, endemic fluorosis will continue to be a dental hazard to a large population in many communities in this country. (Am. J. Pub. Health, Dec. '47 - F. J. Maier)

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A Preliminary Report Concerning DDT Dusting and Murine Typhus Fever in Nine Southeastern States: On 1 July 1945, an expanded typhus control program

in the 9 southeastern states with the highest incidence of typhus in the United States was inaugurated. The program involved primarily the application of 10-percent DDT dust to rat runs, burrows, and harborages in an attempt to control human murine typhus fever cases by reducing rat fleas and other rat ectoparasites. The United States Public Health Service, Office of Malaria Control in War Areas, assisted State Health Departments in expanding, recruiting, and training personnel, and in conducting promotional activities from July to December 1945. A few dusting projects were established in July 1945, and more were added with time so that by March 1946 the full program was in operation. Projects were operated by 122 of the highest typhus-reporting counties in the 9 states during the entire calendar year 1946 and the first half of 1947. These counties in 1944 accounted for 72.3 per cent of all typhus reported in the 9 states or 70.5 per cent of all typhus reported in the entire United States. The remaining 460 counties in these states had no regular DDT dusting programs.

In computing the data from the results of the program, the year 1944, the first complete year prior to inauguration of the expanded dusting program, has been considered as a precontrol or base year for comparing subsequent years. No consideration has been given to other typhus control measures in the dusted or the untreated counties, such as rat-proofing, rat eradication, general sanitation activities, or other insect and rodent control measures. Such activities might conceivably explain an apparently normal or spontaneous decrease in typhus.

Although not much reduction was expected during the organizational period of July-December 1945, a decrease of 10.7 per cent in reported typhus occurred for the year in the dusted counties compared to an increase of 14.5 per cent in the nondusted counties, a differential of 25.2 per cent. A greater differential occurred in 1946 and continued in the first half of 1947, 44.1 per cent and 56.4 per cent respectively. In the 10 counties with the highest incidence of typhus, the reported cases decreased from 1,074 in 1944 to 395 in 1946 and, in several cases, DDT dusting was the only control measure being applied. Reduction of Xenopsylla cheopis, the Oriental rat flea, averaged 84 per cent in the treated areas on the basis of actual flea counts from over 17,000 live rats. (Pub. Health Reps., 9 Jan '48 - J. S. Wiley)

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Warning re Use of CCl_4 to Extinguish Fire: In a letter to the editor in a recent issue of Chemical and Engineering News, R. Gilmont tells of an explosion in an engraving shop that resulted from trying to put out a wax fire with carbon tetrachloride. As the tetrachloride hit the burning wax, a flash explosion caused serious burns to the technicians. An explanation of the mechanism appeared in an article by R. O. Bolt in the 30 June 1947 issue of Chemical and Engineering News. The explosion is a catalyzed reaction between the halogenated hydrocarbon and the ethylenic unsaturation in the presence of a peroxide. All these factors were present in this case since the peroxide in the wax was the result of oxidation of the ethylenic products by the atmosphere. Carbon tetrachloride

should not be used indiscriminately in putting out fires such as burning wax or oil. (Indust. Hyg. Digest, Oct. '47)

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Protection Against Roentgenization: The National Bureau of Standards in its Technical News Bulletin for August 1947 states that it is engaged in an extensive program for determining the effectiveness of concrete as a protective barrier against million volt wide-beam x-rays, the use of which is increasing in medicine and in industry. One basic aim is to determine the highest degree of protection at the lowest cost of installation. A one and one-half million volt x-ray machine in the Bureau's laboratories has been converted so that it will produce beams of varying width, and mounted so as to direct them downward into a "radiation pit." Measuring instruments in the pit can be shifted by remote control, and the entire apparatus is operated from a safe distance and with protection by concrete. Auxilliary protective devices such as lead aprons, lead rubber gloves, lead glass windows, and wall plasters loaded with lead or barium, are also under test. As a result of the study, the finest grades of lead protective glasses are now produced in the United States. New problems are now encountered with the advent of the betatron operated at from 50 million to 300 million volts. (Indust. Hyg. Digest, Oct. '47)

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Reports on USN Research Projects:

Effect of Temperature and Operation Time Upon the Production of Noxious Gases from Silicone-Insulated Electrical Equipment under Conditions of Simulated Submarine Operation. A new group of silica base plastics called silicones has been made available for industrial and military use.

Silicone-insulated electric motors were tested for periods of 96 hours during continuous operation in an airtight chamber under conditions intended to simulate submarine operation. Motor insulation temperature and amperage expressed as a percentage of the rated amperage were measured. The chamber air was analyzed for oxygen, carbon dioxide, carbon monoxide, phenol and formaldehyde. On the basis of the CO concentration in the air and the ratio of air volume to blood volume the carbon monoxide hemoglobin concentration to be expected in the blood of submarine crew members was calculated. Analysis of the chamber air showed that CO was the only substance occurring in undesirable concentrations, and its concentration varied directly as the motor temperature and the duration of the test. With a motor temperature of 200° C. the air CO concentration reached 110 ± 50 p.p.m. which gives 12 ± 5 per cent COHb in the blood of exposed crew members. On the basis of these calculations, as well as the state of health of exposed rats and human subjects, 200° C. was considered to be the maximum motor temperature compatible with health during periods of exposure as long as 96 hours. The results obtained were

appreciably altered by the phenomenon of "curing." "Burn-out" tests indicated that it is not safe to operate silicone-insulated motors at insulation temperatures above 300° C. even for short periods of time. In a 96-hour test with an insulating temperature of 185° C., two men showed no ill effects. In this test the CO concentration in air reached 38.9 p.p.m. and that in blood reached 5.1 per cent COHb. (Proj. X-755, Rep. No. 1, 9 Dec. '47, Nav. Med. Res. Inst., Bethesda, Md. - T. E. Shea, Jr. et al.)

Effects of Storage on Potability of Canned Emergency Drinking Water. Thirty 11-ounce (325 ml.) cans of emergency drinking water, selected at random from storage warehouses in the continental United States, were submitted to the Naval Medical Research Institute for tests of purity and fitness for human consumption. The water had been canned late in 1943 or in early 1944 in cone top beer cans and had been freshly distilled at the time of canning. An inert gas such as nitrogen was not used to replace the air above the water in the cans. The cans were lined with a vinyl acetate and chloride resin of approximately 5 or 6 mg. per square inch thickness; the cap was sealed to the can with butyl acetate resin.

It was found that from a chemical and bacteriologic standpoint, the water remaining within the cans might be used safely for emergency drinking water. Even though the water was not acceptable from a color standpoint, this color in no way affected odor or taste; in fact in some respects the highly-colored water was more acceptable than the flat-tasting, distilled water used for comparison.

Since 20 per cent of the cans were empty or nearly so, and since the remainder of the cans were so badly corroded along the bottom and side seams that a sudden jar caused leaks to develop, the problem is one of availability of water and not potability. All of the cans received for tests had been kept in undisturbed storage. Consequently, it is anticipated that many more cans would have lost their contents had they been subjected to conditions existing at sea. (NM 011 015, Rep. No. 2, 22 Dec '47, Nav. Med. Res. Inst., Bethesda, Md. - W. V. Consolazio)

NOTE: Those interested in seeing copies of the complete reports should address their request to the research activity from which the report originates. Reference may be made to those reports in the same way as to published articles, noting authors, title, source, date, project number, and report number.

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Training in Medical Statistics: Applications are invited from medical officers of the regular Navy who desire assignment to a course of instruction leading to the degree of Master of Public Health with a major in medical statistics. The course is of eight months' duration, beginning 23 September 1948, and is offered by the School of Hygiene and Public Health of the Johns Hopkins University. The curriculum includes required courses in bacteriology, parasitology, epidemiology, biostatistics, and public health administration, but a large part of the student's time is left free for elective courses or investigative work in any of those fields. Applicants who are assigned to the course will be expected to elect such courses in biostatistics as are offered, but will also be able to pursue their interests in related fields. The course offers excellent opportunities for medical officers interested in research in laboratory, field, or clinical medicine, and will provide a good basis for assignment to such duties. Candidates completing the course may expect assignment to research units, schools, BuMed, or to fleet billets requiring a background in medical statistics.

The quota for the Bureau of Medicine and Surgery is two. Applications should be prepared and forwarded to BuMed, as outlined in the News Letter dated 23 May 1947, page 23, and must include a three-year service agreement. (Professional Div., BuMed)

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Separate Ratings Established for Navy Enlisted Dental Technicians: The Secretary of the Navy, by All Ships and Stations Letter 47-1162 dated 15 Dec 1947, established separate ratings for dental technicians as part of the post-war enlisted rating structure which will become effective 2 April 1948.

The general service dental ratings, for peacetime use, will be:

Dental Technicians	(DT)	-	pay grades 4 - 1
Dentalman	(DN)	-	pay grade 5
Dental Apprentice	(DA)	-	pay grade 6

The emergency service dental ratings, for use only during national emergencies, will be:

General Technician	(DTG)	-	pay grades 4 - 1
Prosthetic Technician	(DTP)	-	pay grades 4 - 1
Repair Technician	(DTR)	-	pay grades 4 - 1

(Pay grades 5 and 6 are the same as for general service ratings).

The postwar enlisted ratings have been organized into the following 12 occupational groups:

I Deck	VII Engineering & Hull
II Ordnance	VIII Construction
III Electronics	IX Aviation
IV Precision Equipment	X Medical
V Administrative & Clerical	XI Dental
VI Miscellaneous	XII Steward

The establishment of a dental rating is an important advancement in naval dentistry and a definite improvement in the status of enlisted dental personnel. Their training courses will cover subjects that relate to their daily duties. They will be examined for advancement in dental subjects and compete for advancement only with other men holding dental ratings. Training manuals for this new rating are in the process of preparation and will be distributed as soon as possible. (Dental Div., BuMed)

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Methylrosaniline Chloride, Disposition of Certain Lot Numbers: Laboratory examination of Methylrosaniline Chloride Tablets, JAN #1-289-485, revealed that those with lot numbers, 10548, 10914, 10923, 11262, and 11183 (all manufactured by National Aniline Division, Allied Chemical and Dye Corporation) showed insufficient disintegration in artificial pancreatic fluid. They are therefore considered to be unsuited for use. Accordingly, all quantities of stock of this item, JAN #1-289-485, bearing the above lot numbers, should be surveyed and destroyed. (Materiel Div., BuMed)

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Training in Aviation Medicine: Applications for training in aviation medicine are requested from medical officers of the regular Navy in the rank of lieutenant commander, lieutenant, and lieutenant (j.g.). At present three classes per year with attendance limited to 20 medical officers in each class are planned. The next class will be convened at the School of Aviation Medicine, NAS, Pensacola, Florida, 3 May 1948.

The course of instruction is divided into two phases, first phase, medical, and second phase, aeronautical. The medical phase, which constitutes advanced professional work, includes lectures, laboratory work, clinical work, and demonstrations in ophthalmology, neuropsychiatry, otolaryngology, physiology, psychology, hygiene, cardiology, medical administration, radiological safety, acceleration, use of the low pressure chamber, night vision, and voice communication. The aeronautical phase covers by lectures, practical demonstrations, and films the following subjects: aerology, gunnery, principles of flight, engineering, communications, parachutes, photography, navigation, and essentials of the Naval Service.

Following completion of the first phase those students who qualify will be assigned to the second, or aeronautical, phase, and along with attendance at ground school will receive flight training in basic type aircraft, Link Trainers, multi-engine patrol planes, and service type seaplanes. The training is broad and provides an adequate background in the various phases of aviation. This includes familiarization with gunnery, night observation, formation, dive bombing, rocket firing, navigation, and oxygen flights. Included also will be experience as a passenger in carrier landing and take-off. Medical officers, upon successful completion of the entire course of training, are designated as Naval flight surgeons and receive their wings.

Flight surgeons have the opportunity to serve in some of the most interesting billets in the Navy. These include duty aboard aircraft carriers, with Combat Air Groups, with the Naval Air Transport Service, in Marine Air Wings, in multi-engine patrol squadrons, and at air stations, both continental and overseas. Other important opportunities for service with the aeronautical organization are offered by the ever expanding field of aviation medical research which is currently concerned with the physiological and psychological problems involved in flying the high performance planes of today and tomorrow. Centers for this research are the Naval Medical Research Institute, Bethesda, Maryland; the School of Aviation Medicine and Research, NAS, Pensacola, Florida, and the Naval Air Material Center, Philadelphia, Pa. There are many other interesting aspects of a career in Naval aviation medicine.

Further opportunities for graduate specialized training in basic sciences and clinical fields allied to aviation medicine will be offered flight surgeons who desire to pursue such further training.

With smaller classes and a lengthened curriculum this course becomes even more desirable than heretofore. Applications for this course are now being received. Submit your request to: Bureau of Medicine and Surgery, Navy Department, Washington, D. C. (Professional Div., BuMed)

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Course in Medical Department Logistics: A two-day intensive course in Medical Department Logistics will be given on 16 and 17 February 1948 at the U. S. Naval Medical School, Bethesda, Maryland.

Medical officers of all ranks of the Reserve and regular Navy are invited to attend. Those interested may request authorization orders (no expense to U. S. Government). (Professional Div., BuMed)

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Reporting on Dental Roentgenograms: Dental officers are required to submit a NAVMED-K (Rev. 5-47), REPORT OF DENTAL OPERATIONS AND TREATMENTS, each month for all authorized dental operations and treatments

which have been accomplished. This includes dental roentgenograms for persons for whom dental treatment is authorized. The availability of dental treatment by dental officers of the Navy is defined in paragraph 1357.1 of the Manual of the Medical Department. The limitations of dental treatment authorized for dependents are defined in a decision of the Judge Advocate General of the Navy; JAG:II:WG:mh, P16-3/OD, dated 22 March 1946. Dental service is not authorized for outpatient dependents. Dental roentgenograms made for dependents, other than those which are made for inpatients, must not be included in the NAVMED-K (Rev. 5-47). To do so would defeat the purpose for which the report is required. The manner in which emergency dental treatment for humanitarian reasons must be reported by dental officers is contained in paragraph 5112.4 of the Manual of the Medical Department, (Dental Div., BuMed)

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Deterioration in Neosynephrine Hydrochloride Solution, 1%, JAN #1-300-810: Laboratory reports on samples of subject item submitted to the Bureau for examination reveal that in some instances there is evidence of deterioration manifested by discoloration and precipitation due to oxidation. Therefore, prior to use, stock of this item should be examined for evidence of deterioration and if any is found, it should be surveyed and destroyed. (Materiel Div., BuMed)

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Reporting Epidemics of Diarrheal Diseases: BuMed Circular Letter No. 47-62 of 12 May 1947 directs that copies of reports and subcultures concerned with outbreaks of diarrheal disease be submitted to the Naval Medical Research Institute, the Bacteriology Facility of which is the central coordinating agency for this class of disease. It is recommended that duplicates of cultures which are forwarded be retained by the originating activity until confirmation of identification is received; such a procedure will guard against complete loss of organisms in the event of accidents in transit.

In order to be in a position to lend assistance it is necessary that the coordinating agency be adequately informed of field conditions. It is requested, therefore, that upon the recognition of an outbreak of diarrheal disease all ships and stations forward promptly to the Bacteriology Facility, Naval Medical Research Institute, Bethesda, Maryland, an information copy of the DISPATCH REPORT now required as shown in the Manual of the Medical Department, Paragraph 35 D 1.1 (b), page 415. (Preventive Medicine Div., BuMed)

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New Advanced Training in Aviation Medicine: An unusual opportunity for advanced training in aviation medicine is being made available to medical officers of the Navy. The Bureau of Medicine and Surgery has established a postgraduate training program to fill a need for specialists in research in aviation physiology.

Medical officers selected for this training who are not flight surgeons will first be given the regular course in aviation medicine. Selected applicants will then be given a graduate course in physiology leading to an MS degree. A course has already been established at the University of Southern California. The special tools for research in aviation physiology (including a human centrifuge and a low pressure chamber) have already been installed there.

Upon successful completion of the requirements for an MS degree, selected medical officers will have an opportunity to continue their studies in naval or civilian laboratories and become candidates for PhD degrees.

The interest and imagination of medical officers will be challenged by the problems awaiting research. For example, it is imperative that medical officers define human tolerance to changes in high velocity and the environment of high altitudes. Equipment must be devised to increase human tolerances to acceleration and high altitudes. The human limits in aircraft performance, and the point at which piloted aircraft must give way to guided missiles, must be determined. The physiological effects of rocket take-offs, high acceleration catapult shots, catapult crashes, seat ejection, parachute opening, and aircraft crashes are awaiting investigation. Laboratory investigations must be made with human centrifuges, high speed crash catapults, drop towers, ejection seat towers, orientation and acceleration devices, and low pressure chambers. New laboratory equipment must be designed.

Aviation physiologists must determine the anatomical and physiological limitations of man; they must determine how high and how fast the pilot can go. Then they must help improve airplane design and increase flight safety and comfort.

This is an invitation for you to apply for postgraduate training in order to qualify for study in problems in aviation medicine. Applications are desired by 15 March 1948 from medical officers of the regular Navy and from Reserve officers who have applied for commissions in the regular Service. Applicants should be of the rank of lieutenant commander or below. The application must contain an agreement not to resign during the course or within three years after its completion. (Professional Div., BuMed)

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ALNAV 3 13 January 1948

Subj: Medical Records in Connection with Promotion

Following sections Naval Courts and Boards have been changed as indicated: Section 863, new sentence added which provides that signed report of physical examination shall be submitted in duplicate on Form Y and appended to record. Section 865, modified so that medical history as set forth in current health record shall be considered in connection with examination.

--SecNav

NOTE: In accordance with Section 865, Naval Courts and Boards, the Bureau of Medicine and Surgery was obliged to furnish to various Boards of Medical Examiners a copy of the medical record, since last permanent promotion, of each officer who had been selected for promotion. AlNav 3, above, eliminates this procedure and directs the Boards of Medical Examiners to make reference to the current health record in connection with the physical examination, and to submit the results of the physical examination in duplicate on Form Y and appended to the record of proceedings. It was considered that the medical records submitted to the Boards of Medical Examiners in the field served little purpose inasmuch as the record had already been reviewed by the Selection Board in Washington, and the Boards of Medical Examiners in the field have in their possession the officer's current health record which contains an abstract of his medical history. This change in procedure saves hundreds of man-hours and thousands of dollars by reason of not having to prepare photostatic, microfilm or typewritten copies of the medical records concerned.

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BUMED-4123-FHT, NH73/A1-1 20 January 1948

To: Secretary of the Navy
Via: (1) Chief of the Bureau of Yards and Docks
(2) Chief of Naval Operations

Subj: Disestablishment of the U. S. Naval Hospital, Dublin, Georgia - Disposition of

Refs: (a) SecNav ltr - Serial: 748P24, dtd 29 December 1947.
(b) BuMed ltr - BUMED-41-MFD, NH73/A1-1, dtd 3 December 1947, to SecNav, via CNO.

Pursuant to reference (a) which approved the disestablishment, effective 30 June 1948, this letter from the Chief of BuMed states that (1) by reference (b), paragraph (2), the full facilities of this hospital have been offered to the

Veterans Administration, and (2) the Veterans Administration has requested funds and personnel allocations to permit assumption of operation on 1 July 1948; and requests that the necessary steps for transfer of the subject hospital to the Veterans Administration, on 1 July 1948, be effected.

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Circular Letter 48-6 19 January 1948

To: Comdts, NDs, Continental U.S.; Comds, NavTraCens; ComdgGens, MarCorpsBaks; CO, NavTraSta, NavBase, Newport, R.I.; Supt., NavAcad, Annapolis, Md.

Subj: Tuberculin Testing of Recruits - Availability of Material for

Ref: (a) BuMed C.L. No. 47-91 dtd 16 July 1947

This letter from the Chief of BuMed states that the new "Single Strength" tuberculin test material is available for issue from the Naval Medical Supply Depot, Brooklyn, and Naval Medical Supply Depot, Oakland, only to those training activities addressed and authorized to administer the test to recruits.

The catalog descriptions of the new tuberculin test material will be changed to read:

1-613-975 Tuberculin Tests, Single Test Strength, 50s: Package contains 0.005 mg. purified protein derivative and 5 cc. buffered diluent; when diluted each 0.1 cc. contains 0.0001 mg. purified protein derivative. (Navy--To be used only in special surveys where the usual "First" and "Second" test strength procedure is not required.)
Unit: Pkg.

1-613-980 Tuberculin Tests, Single Test Strength, 250s: Package contains 0.025 mg. purified protein derivative and 25 cc. buffered diluent; when diluted each 0.1 cc. contains 0.0001 mg. purified protein derivative. (Navy--To be used only in special surveys where the usual "First" and "Second" test strength procedure is not required.)
Unit: Pkg.

Instructions are given in the letter concerning (1) the requisitioning of the test material and (2) the care of the syringes used in administering the tests.

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